Break-Out Session 4

Database Development for Safety and Efficacy Biomarkers

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Overview

- Hypothetical case study (genomic data submission), presented in 4 steps
- Each step includes a 5 min. presentation of a specific tool, relevant to the step, but not necessarily connected to case study itself: idea is to “translate” the tool to the case and identify gaps, etc.
- Interactive: Please ask questions and provide comments at every point in time

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BO4: Case Study Background

- Drug X being developed for treatment of a solid tumor
- Tumor tissue has a characteristic gene expression pattern when compared to normal tissue
- This signature is detectable as early as two weeks after disease onset
- Signature remains constant for first weeks of disease, then changes, likely due to other pathophysiologic events related to the disease

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BO4: Case Study Background

- Company decides to:
  1. Determine if characteristic signature can be obtained from peripheral blood
  2. Explore whether or not signature can be used as efficacy biomarker (i.e. changes after drug treatment)
- To discuss this approach and early results, the company submits a VGDS

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BO4: Case Study Data Submission

- VGDS Study:
- 200 patients:
  - Patients split into 150:50 for treatment and placebo (best of care)
  - PBMCs collected at t=0, 8, 16 and 24 weeks)
- 200 controls:
  - PBMCs collected (disease – normal comparison)
- RNA isolated from PBMC and analyzed on high-density DNA microarrays

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5 Minute Presentations

- Data Submission
  - Usha Reddy: HL-7, CDISC
- Data Analysis
  - Weida Tong: ArrayTrack
- Data Interpretation
  - Shashi Amur: SafeBase
  - Jennifer Fostel: CEBS
- Future Development
  - Felix Frueh: PGx Suite

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BO4: Case Study
Data Submission - Questions

- What data should be submitted?
  - raw data (*cel file, probe set file, image data)*
  - normalization algorithm
  - list of genes
  - biological interpretation of the data
  - MIAME guidelines
  - phenotypic information
- How can we link the submitted microarray data back to phenotypic data: what types of databases are needed and do they exist (i.e. gene expression signature to phenotype relationship)?
- What other guidelines currently under development should be followed to capture both microarray and phenotypic data?
  - HL-7/CDISC
  - MAQC
  - ERCC

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BO4: Case Study
Data Analysis

- Data set loaded into data analysis tool
- Statistical analysis carried out to identify differentially regulated genes:
  - At baseline (cancer vs. normal)
  - During treatment (4 time points, treated vs. placebo)
- Different analysis platforms used by Sponsor and FDA
- Significant changes observed by Sponsor and FDA, but overlap of gene list varied in different cases

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BO4: Case Study Data Analysis - Questions

- What are the best practices for the normalization of hybridization data?
- What are the best practices for the statistical analysis of normalized hybridization data for changes in gene expression relative to control samples?
  - Stringency
  - P-value vs. fold change
  - False Discovery Rate and other statistical tools
- What are the best practices for the statistical analysis of normalized hybridization data for signatures associated with baseline expression levels?
  - Supervised learning methods
    - Consensus methods
    - Single classification models
- Unsupervised learning methods

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BO4: Case Study Data Interpretation

- The gene signatures obtained after the data analysis were used for further biological interpretation
- The goal of this effort was to
- Compare the reconstruction analysis at the FDA with the analysis submitted by the sponsor
- Generate additional useful information from the data consistent with interpretations generated by the sponsor and the FDA
- The patient vs. control comparison did not reveal any interesting affected pathways, but the treated vs. untreated comparison showed activation of apoptosis and chemokine pathways in patients treated for 8 or more weeks.

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BO4: Case Study
Data Interpretation - Questions

- Are the tools used sufficient to get biological interpretation?
- What other tools (such as GeneGo, BioCarta, KeyMolnet), should be used?
- How should the biological interpretation of gene expression data be used in a regulatory context?
- Based on this data, is it reasonable to expect that gene expression analysis of PBMCs represents gene expression changes in oncology?
  - Signatures to predict time to death (TTD) and time to progression (TTP)
  - Signatures to predict drug response.
  - What other therapeutic areas do we know about where PBMCs are good surrogate reporter cells?
- Should data analysis tools and databases (knowledge bases) be integrated?

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BO4: Case Study
Future Scenario

- Creation of the ultimate pharmacogenomics suite ("Genomics Office" – what should it look like?
  - Cover early data capturing, incl. clinical, analytical, experimental, etc.
  - Provide operational links to variety of analysis tools, no data conversion necessary
  - Link to other "-omics" fields
  - Link to online databases, e.g. HapMap, etc.
  - Link to adverse event databases, e.g. AERS etc.

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BO4: Case Study
Future Scenario - Questions

- Can we capture all this in a single application or is there a need for independent, but linked platforms?
- Can the analysis and interpretation be automated?
- How can the System approach play a regulatory role?

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